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(54) Title: READILY-ABSORPABLE FATTY ACID EMULSIONS

(57) Abstract

The compositions are oil-in-water emulsions which are prepared by emulsifying a vegetable or animal oil rich in polyunsaturated, long-chain fatty acids with an emulsifying agent in the presence of one or more polyhydric alcohol stabilizers, and antibacterial or antifungal preservatives. Oil-soluble nutrients, such as the naturally-occurring amino acids, vitamins and their analogs may also be included in the emulsions, as well as minor amounts of coloring and flavoring agents. Buffers may also be included when necessary.

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READILY-ABSORPABLE FATTY ACID EMULSIONS

BACKGROUND OF THE INVENTION

Complex foods are broken down to simple molecules by the process of digestion. The proximal intestine is the major site of absorption for iron, calcium, water-soluble vitamins and fats. Long chain triglycerides are ingested in the diet. Bile acids secreted by the gall bladder emulsify these water-insoluble lipids in the small intestine, thereby greatly increasing the surface area of the molecules and enhancing the activity of pancreatic lipase. In the lipolytic phase, lipase splits the food triglycerides into monoglycerides and fatty acids.

Certain polyunsaturated fatty acids are essential dietary components since they cannot be manufactured by the body. Among the essential fatty acids, linolenic acid, di-homo-gamma-linoleic acid and arachidonic acid have been shown to be neessary for the tissue biosynthesis of the prostaglandins, which perform vital hormone-like activities in the transmission of genetic information in all cells. For example, the blood vessel endothelium is the cite of biosynthesis of a prostaglandin known as PGI_2, which functions to maintain the integrity of blood vessel walls and thus prevent the adherence or aggregation of platelets which may lead to

clotting and other thromboembolic disorders. Other prostaglandins have been shown to be necessay to maintain the optimal tone of bronchial tissue and to regulate blood pressure. Many long-chain unsaturated fatty acids have been shown to be biosynthetic prostaglandin precursors, i.e. arachidonic acid is the direct biosynthetic precursor of PGI_2.

The bile acids agregate the fatty acids into micelles of a diameter of about 25 angstroms which are solubilized in water. In the mucosal phase of the intestine, the lipid contents are absorbed and long chain fatty acids of greater than ten carbon atoms are reesterified intracellulary and formed into chylomicrons of less than 0.5 micrometers in diameter, by the conjugation with lipoproteins, phospholipid and cholesterol. As chylomicrons, lipids pass through the epithelial cells and basement membrane, eventually finding their way into the central lacteal of the villi of the small intestine. From there, the chylomicrons are secreted into the lymphatic system, passed through the thoracic duct and emptied into the portal venous system.

Any disorder which decreases the ability of the pancreas to excrete lipase results in the malabsorption of fat. Pancreatic exocrine insufficiency results in severe cases of lipid malabsorption. Chronic pancreatis due to alcoholism and cystic fibrosis are the most common causes of this insufficiency. Pancreatic carcinoma may also cause malabsorption if the pancreatic duct is occluded.

A deficiency in bile acids causes a decrease in the activity of lipase. Any disorder which decreases the synthesis, secretion or reabsorption of bile acids can result in fat malabsorption by impairing emulsification and micelle formation. Such disorders include liver

disease, intrahepatic cholestasis, bile duct occulsion, bacterial overgrowth in the small intestine and inflammatory or infiltrative diseases of the small intestine.

Such conditions lead to the malabsorption of fat-soluble vitamins, in multiple deficiencies. Vitamin K deficiency causes impaired blood coagulation. Vitamin A deficiency causes night blindness and loss of the integrity of the epitelial membranes and connective tissue. Vitamin D deficiency along with malabsorption of protein and calcium results in osteomalacia.

Even when the concentration of bile acids is not pathologically decreased, it may be desirable to enhance the lymphatic absorption of fatty acids and fat-soluble vitamins and other biologically-active agents. For instance, orally-ingested 13-cis-retinoic acid, a Vitamin A analog, has been shown to accomplish the prolonged remission of cystic and conglobule acne. Increased serum vitamin A has alleviated conditions such as type II hyperlipoproteinaemia, postilectomy diarrhoea, and osteomalacia. See D. L. Barnard, Gut, 14, 316(1973). Vitamin A and Vitamin E and their analogs may play a role in the protection of cells from carcinogens. See M.B. Sporn, et al, Federation Proc., 35, 1332 (1976). Fatty acids have been shown to suppress serum cholesterol and have been asserted to be useful for the treatment of thromboembolic disorders. Vitamin K apparently acts to enhance the action of cytotoxic agents useful in chemotherapy.

It is therefore an object of the present invention to provide a composition which will enhance the lymphatic aborption of naturally-occurring essential fatty acids.

It is another object of the present invention to provide a means for enhancing the intestinal absorption of fat-soluble

vitamins, vitamin analogs and other biologically-active agents.

Still other objects and advantages of the present invention will be apparent from the description and appended claims.

BRIEF DESCRIPTION OF THE INVENTION

The objects of the present invention are accomplished by the oral administration to a human or other mammal of oil-in-water emulsions which are formulated so as to contain effective amounts of essential fatty acids, such as linoleic, linolenic and arachidonic acid, in a physical form which is readily absorbed into the lymphatic system and thus into the blood stream. The emulsions of the present invention are also useful to enhance the absorption of vitamins, particularly the oil-soluble vitamins and their analogs. Other oil-phase soluble pharmaceuticals may also be effectivly delivered to the blood stream via the present compositions. The compositions of the present invention also greatly reduce, or eliminate the need for the fat emulsification by bile acids, since the emulsions are prepared so that the oil-phase droplets are of a diameter equivalent to or less than the average diameter of the naturally-formed lipoprotein chylomicrons, i.e. up to about 0.5 micrometers.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention are oil-in-water emulsions which are prepared by emulsifying a vegetable or animal oil rich in polyunsaturated, long-chain fatty acids with an emulsifying agent in the presence of one or more polyhydric alcohol stablizers, and antibacterial or antifungal preservatives. Oil-soluble nutrients, such as the naturally-occurring amino acids, vitamins and their analogs may also be included in the emulsions, as well as minor

amounts of coloring and flavoring. Buffers may also be included when necessary.

The animal or vegetable oils useful in the emulsions of the present invention include those which contain a high proportion of unsaturated C_{12}-C_{18} fatty acids to C_{14}-C_{18} saturated fatty acids, since it is the polyunsaturated fatty acids which have been implicated in the in vivo biosynthesis of biologically active prostaglandins. The preferred oils possess an unsaturated fatty acid to saturated fatty acid ratio of from about 10:1 about 5:1. Preferred vegetable oils include primrose oil, safflower oil, sunflower oil, sesame oil, cottonseed oil, etc. Of the vegetable oils sesame oil is especially preferred, since it can be readily stablized by natural emulsifying agents at an effective droplet size for rapid gut absorption. Fish oil is the preferred animal oil for the formation of the present emulsions, since it contains large amounts of eicosapentaenoic acid (EPA), a PGI precursor.

The vegetable or animal oil or mixture of oils will make up the major proportion of the oil phase of the present emulsions, and preferably will comprise 5-45% by weight of the entire emulsion, most preferably about 10-30%.

The oils are suspended in water to form the emulsions of the present invention by means of one or more emulsifying agents. Any non-toxic, pharmacologically-acceptable emulsifying agent may be employed in emulsions, such as those discussed in Remington's Pharmaceutical Sciences, A. Osol, ed., Mack Pub. Co., Boston, Mass. (16th ed., 1980) at pages 310-321 and 1243-1248, the disclosure of which is incorporated by reference herein. Preferred emulsifying agents are the natural surfactants, which function by coating oil-phase droplets with a multimolecular film so as to accomplish the necessary dispersion. Multimolecular film-forming agents are preferred due to their ability to form strong, coherent films

which render them highly resistant to coalescence, even in the absence of a well-developed surface potential. Especially preferred natural agents include acacia (HLB ca. 8.0), gelatin (HLB ca. 10.5), tragacanth (HLB ca. 13.2), carrageenan, chrondus and pectin and mixtures thereof. Alternatively, or in combination with the foregoing, other conventional emulsifying agents can be employed -- such as polyhydric fatty acid esters. In accordance with known techniques the HLB of the emulsifier, or emulsifier combination is adapted to be compatible with the requirements of the oil phase. Preferably the emulsifying agent or agents will comprise from about 5-40% by weight of the emulsion, preferably 10-30%, wherein the sum of the oil and emulsifier is about equal to or less than the amount of water in the emulsion.

Stabilizing agents are also used in the emulsions of the present invention. They function to increase the viscosity of the aqueous phase, thus stabilizing the emulsion, and to prevent the precipitation of the emulsifying agents by dissolved metal salts which may be present. Useful stabilizing agents may be selected from any of those known to be compatible with the emulsifying agents used, and include fatty alcohols, methyl cellulose, hydroxypropyl celluloses and the like. An especially preferred class of stabilizing agents is the C_2-C_8 polyhydric alcohols, i.e. glycerin, sorbitol, and mixtures thereof. These nontoxic agents are easily absorbed in the intestinal tract and may aid the absorption of other components of the emulsion. The stabilizing agents will comprise from about 1-20% by weight of the emulsions of the present invention, preferably from about 5 to 10%.

The emulsions of the present invention will include a water-soluble buffer system, i.e. an organic acid and acid salt pair, in an amount effective to stabilize the pH of the emulsion so as to protect intestinal flora and to offset the

effect of added nutrient acids. A preferred organic buffer system for use in the compositions of the present invention is about a 3:1 ratio of citric acid-sodium citrate.

When present, the buffering chemicals will make up about 0.25-2.5% by weight of the emulsion.

The emulsions of the present invention will also include minor but effective amounts of antibacterial and antifungal agents which act to maintain the emulsion in a sterile condition. Preferred antibacterial agents are the (C_1-C_4) lower alkyl 4-hydroxybenzoate esters such as methyl and propyl 4-hydroxy benzoate and mixtures thereof. Sodium benzoate is a preferred antifungal agent. These antimicrobial agents will preferably make up about 0.05-1% by weight of the emulsion.

The oil phase of the present emulsions may also be used to solubilize and deliver dietetically- and therapeutically-effective amounts of oil-soluble nutrients and pharmaceuticals. One preferred class of nutrients is the fat soluble vitamins which comprise vitamins A, D, E and K and their biologically-active derivatives and analogs. These vitamins may be incorporated into the present emulsions in amounts which will vary in accord with accepted medical practice, both for the alleviation of dietary deficiencies and for therapeutic applications, such as those discussed hereinabove. Fat soluble vitamins useful in the practice of the present invention include vitamin A (retinol, trans-retinoic acid, 13-cis-retinoic acid, retinol-acetate, retinol palmitate). The present emulsions may be formulated so as to deliver from about 2000 - one million USP units of these compounds per dose of emulsion (i.e. about one-half teaspoon).

Another useful fat-soluble vitamin is vitamin E and its derivatives, i.e. d or dl-alpha-tocopherol, the alpha-

tocopheryl acetates and succinates. The present emulsions may be formulated so as to comprise about 20-10,000 USP units ("IU units") of these compounds per dose of emulsion, preferably 250-600 USP units per one-half teaspoon dose. Vitamin E compounds such as alpha-tocopheryl acetate also function as antioxidants to stabilize the unsaturated fatty acids present in the animal or vegetable oil component of the emulsion, and also act to stabilize any vitamin A present against oxidation. Additional antioxidants, such as minor amounts (i.e. .025-.5%) of ascorbyl palmitate, may also supplement the antioxidant function of vitamin E or fulfill this function in its entirety. Vitamin D1,2,3 and their fat-soluble metabolites such as 25-hydroxy cholecalciferol and 1,25-dihydroxycholecalciferol may also be readily incorporated in the present emulsions. When the emulsions are adapted as dietary supplements for normal individuals, a maximum dose of 50-500 USP units per dose of emulsion is sufficient. The emulsions may be made more highly concentrated to treat specific pathological conditions, i.e. osreomalacia, hypoparathyroidism or hypocalcemic tetany, in accord with accepted medical practice.

Vitamin K1, K2 and their fat-soluble derivatives such as menadione and phytonadione are also preferred vitamins for incorporation into the emulsions of the present invention which are formulated to contain about 1-50 mg per dose. More concentrated formulations may be prepared and administered if necessary to treat enteric diseases in which vitamin K absorption is inhibited, such as sprue, regional enteritis, enterocolitis, dysentary and the like.

For a general discussion of the oil (fat)-soluble vitamins, including their analogs, utilities and dosages, see Remington's Pharmaceutical Sciences, at pages 948-955, the disclosure of which is incorporated by reference herein.

The emulsions of the present invention may also include minor but effective amounts of one or more amino acids. Especially preferred are those amino acids which have immunostimulatory activity, i.e. l-lysine, l-arginine or mixtures thereof. Preferably, the amino acids will be present in an amount sufficient to provide about 5-15 mg per dose of emulsion, or in an amount equal to about 0.25-2% by weight of the emulsion.

The emulsions of the present invention will also optionally comprise a minor but effective amount of coloring and flavoring. Suitable flavoring agents are described in Remington's Pharmaceutical Sciences at pages 1229-1239, the disclosure of which is incorporated herein by reference.

Accordingly, preferred emulsions formulated in accord with the present invention would comprise about 20-50% of an oil phase incorporating about 10-30% of unsaturated fatty acid-containing vegetable or animal oil, about 10-30% of an emulsifying agent, about 1-20% of one or more stabilizing agents dispersed to a particle size in the chylomicron range in about 30-80%, preferably about 40-55% of water incorporating 0.1-2.0% of one or more antimicrobial preservatives and optionally incorporating minor but effective amounts of amino acids, antioxidants, buffering agents and flavorings, wherein water constitutes the continuous phase (O/W). The amount of the emulsifier is similar to that of the oil, and they are preferably within twenty percent of each other by weight, and are soluble in each other. The combined amount of oil and emulsifier is close to that of the water and usually from one to twenty percent less than the weight of the water. In the preferred embodiments of the present invention, the emulsions will comprise a biologically-effective amount of one or more oil-soluble vitamins or their derivatives, such as vitamins A, D, E or K.

The utility of the present stabilized oil-in-water emulsions is not limited to the effective lymphatic absorption of fat-soluble vitamins, but extends to the delivery of a wide variety of fat-soluble compounds of pharmaceutical interest, including hormones (i.e. steroids), prostaglandins, gastrointestinal drugs, cardiovascular drugs, respiratory drugs, sympathomimetic drugs, enzymes, analgesics, and the pure extracts of edible oils, such as gossypol, eicosapentaenoic acids, dihomolinoeic acids and the like. Emulsification can be achieved by several procedures which use a high shear force to obtain small particle sizes. High shear force relates to the applied forces which cause two contiguous parts of a body to slide relative to each other in a direction parallel to their plane of contact.

High shear force may be achieved by use of a pressure homogenizer. Such pressure homogenizers as, for example, the Gaulin Homogenizer, function by passing a product, under pressure, through a restricted aperture whereupon an instant pressure drop to less than atmospheric pressure occurs. This causes both a shearing action and cavitation bubbles. The product then strikes an impact ring at velocities up to 57,000 feet per minute, further shattering the particles by both impact and implosion of the cavitation bubbles.

In another procedure, a technique involving high-speed mixing (i.e. from about 3,000 to about 12,000 rmp) coupled with a high shear force is used. In this procedure, the effective shear force is dependent on the solids content and the viscosity of the medium being mixed, the speed of mixing, and the geometry of the mixer and the mixing vessel. A type of mixer which achieves this dual function of high speed mixing and high shear force is, for example, one employing a single shaft mixer with two separated, serrated circular horizontal shear plates set between two inverted feed cones on a single shaft. Using a mixer, both high speed mixing and high shear force are rapidly achieved.

Various propeller and turbine agitation systems are commercially available to carry out the emulsification.

The general procedure is to form a first mixture comprising mainly the fatty or oily components and emulsifier. A second mixture is formed comprising mainly the water and water-soluble ingredients. These two mixtures are then combined and subjected to high shear agitation under conditions adapted to provide very small particles, preferably of chylomicron size and smaller.

The emulsions of the present invention in a preferred procedure are prepared by first forming a homogeneous mixture of the vegetable and/or animal oils with the oil-soluble pharmaceuticals, oily antioxidants and amino acids by stirring the ingredients together in a standard slurry-type dispersal mixer with rotor-blade circulating element for 20-30 minutes. The emulsifying agent is then added to the stirred, oily pre-emulsion and stirring continued for 30-60 minutes until a homogeneous paste results. In a separate mixer, a solution of about 70-85% of the stabilizer is combined with the antibacterial agents and heated via an immersion heater to about 70-80° C until dissolution is complete. A 30-40° C solution of the remainder of the stabilizer component in the water containing the flavoring and antifungal agent is then added to the stabilizer-antibacterial solution and vigorous mixing continued for 1-2 hours. This solution is added to the stablized oil phase with slow steady stirring over 10-15 min. A concentrated aqueous solution of the buffering chemicals is then added.

To achieve the necessary fine droplet size, the emulsion is then passed three times through a high pressure homogenizer at about 4000-6000 Psi in a continuous manner. A 25 gallon batch of emulsion can be finished in about 3-4 hours.

The finished emulsion is ready for packaging in standard liquid-dispensing containers. Alternatively, the emulsion may be encapsulated in gelatin capsules or suppositories suitable for oral, buccal, anal or vaginal administration.

The invention will be further described by reference to the following detailed examples.

EXAMPLE I - VITAMIN A/E EMULSION

A stable oil-in-water emulsion containing Vitamins A and E in the oil phase was prepared by the following procedure.

TABLE I

Component	Component Wt. (Grams)
PART A	
Vitamin A Palmitate	616
Ascorbyl Palmitate	19
Vitamin E Acetate	19
Sesame Oil (Refined)	21,610
l-Lysine	500
l-Arginine	500
PART B	

Gum Acacia (Spray-Dried, Vacuum Gassed)	22,800
PART C	
Glycerin	6,650
Methyl 4-hydroxy benzoate	152
Propyl 4-hydroxybenzoate	38
PART D	
Deionized Water	39,360
Sorbitol (70% in water)	2,965
Cherry extract	170
Sodium Benzoate	95
PART E	
Citric Acid	380
Sodium Citrate	125
Water	900
Total	95,899

The ingredients of Part A were combined and stirred in a 30 gal. Lightnin vertical tank, gear-reduced mixer equipped with an 8 inch blade for 25 min. The acacia gum was added with continued stirring for 45 min. until a homogeneous paste results. The ingredients of Part C were combined and mixed

separately at 75° C until they had dissolved. The Part D ingredients were combined, heated to 35° C and the Part C ingredients added with vigorous stirring over 1.5 hours. The resultant stabilizer mixture (Part C plus Part D) was added to the oily pre-emulsion (Part A plus Part B) over 10 minutes while maintaining the stirring at as slow a rate as possible. The ingredients of Part E were combined and the solution added to the stirred mixture with a small amount of water to bring the total batch up to twenty-five gallons. The emulsion was then homogenized to the desired droplet size by three continuous passes through a Gifford-Wood high pressure homogenizer at 5000 psi (Gifford Wood, Inc., Hudson, N.Y.), at the rate of one full pass per hour. The final creamy emulsion was the consistency of runny toothpaste, and was very stable. Upon storage over an extended period of time the components did not separate.

When a few drops of the emulsion were stirred into a 1000-fold excess of water, a homogenous, opaque suspension formed which did not break or separate when allowed to stand for at least a week at 25° C. The emulsion delivered 25,000 USP units of Vitamin A and 400 USP units of Vitamin E per 4.0 ml dose (one-half teaspoon).

EXAMPLE 2

A Vitamin E emulsion was prepared by the procedure of Example 1, omitting the Vitamin A Palmitate. An emulsion similar to that of Ex. 1 was observed.

EXAMPLE 3

A Vitamin A, D3 and E emulsion was obtained by following the procedure of Example 1, but incorporating 5.5 g of Vitamin D3 into Part A. An emulsion similar to that obtained in Ex. 1 was observed.

The emulsion delivered 25,000 USP units of Vitamin A, 400 USP units of Vitamin E and 400 USP units of Vitamin D3 per 4.0 ml dose.

EXAMPLE 4 - ABSORPTION SCREENING STUDY

A screening study was conducted to compare the intestinal absorption of the emulsion of Ex. 3 with that of a standard-type, over-the-counter cod-liver oil preparation containing Vitamins A, D and E, which was dosed with water to prepare an emulsion containing the same proportional USP units of the three vitamins as the emulsion of Ex. 3. Two rats were dosed with approximately 2.5 ml of the Ex. 3 emulsion and two were dosed with 2.5 ml of the cod-liver oil emulsion. Two of the rats were sacrificed 30 min. after administration of the emulsion, and two were sacrificed 2.0 hours after dosing. The rats were sacrificed by exsanguination after carbon dioxide suffocation. Two control animals which had been treated with water and cod-liver oil were also sacrificed and assayed. Cross-sections of the duodenum were taken approximately 1.0 cm from the pylorus, then immediately processed for microscopic examination by sectioning on a freezing microtome.

The frozen sections were stained with Oil Red O and examined microscopically for the presence of fat within the duodenal structure. The amount of Oil Red O staining material, reflecting the amount of absorbed fat, was graded subjectively on a scale of O, 1+, 2+, 3+ and 4+. The results are summarized in Table II.

TABLE II. ABSORPTION SCREENING STUDY IN RATS

(Article, Grade, and Observation)

Control distilled water

Grade 0

No fat globules are recognized within the duodenal structures. Oil Red O staining material is present within the lumen.

Cod liver oil (undosed)

Grade 1+

Occasional Oil Red O staining material is present in the epithelial cell cytoplasms and in interstitial-lacteal areas of the villi.

Dosed Cod liver oil - 30 minutes

Grade 2+

Oil Red O staining globules are present in both the epithelial cell cytoplasm and in the interstitial-lacteal areas. Size of the globules varies considerably, and there is marked variability in the amount (numbers) of globules within the different villi.

Ex. 3 Emulsion - 30 minutes

Grade 2+

Very small Oil Red O stain globules are finely dispersed within the epithelial cytoplasm and a less number

of variable size globules are located in the interstitial-lacteal areas.

Dosed Cod Liver Oil - 2 hours

Grade 2+

Primarily, Oil Red O staining globules are present in the epithelial cell cytoplasms with lesser numbers in the interstitial-lacteal areas.

Ex. 3 Emulsion - 2 hours

Grade 4+

Oil Red O staining globules are very numerous within the epithelial cytoplasm, diffusely throughout the villi, and numerous globules are also present within the interstitial-lacteal areas of the villi.

The results outlined on Table II show that the emulsion of Ex. 3 is more evenly and rapidly absorbed into the interstitial-lacteal areas of the villi of the small intestine of the rat than is an oil-in-water emulsion prepared in a standard manner (i.e. by mixing cod liver oil into water in the presence of additional vitamins). A visual examination of the stained sections indicates that absorption in accordance with the present invention was about 100% greater than that with the conventional formulations after two hours. It is expected that the emulsions of Exs. 1-2 as well as emulsions comprising other fatty oil-soluble pharmaceuticals will behave similarly in this test and that this test protocol demonstrates the high efficiency of the absorption of oils and oil-soluble pharmaceutical agents in

the mammalial lower digestive tract when they are emulsified to produce the compositions of the present invention.

Therapeutic products have been frequently used in the clinical administration of a drug or nutrient together with a suitable oil. It has been postulated that an aqueous emulsion of a water soluble drug may have an enhanced lymphatic directivity due to the presence of an oil. In connection with this mode of administration, due to the normally larger size of the drug particles in an oil emulsion, the drug is maintained in the capillary vessels and gradually permeates into the surrounding tissues over a longer period of time. However, in contrast to prior procedures, the present invention facilitates a rapid and high level of absorption of therapeutic agents.

Accordingly the technique of forming emulsions set forth in this specification is applicable to a wide range of therapeutic agents which are oil soluble and suitable for emulsification. Even water soluble drugs can be adapted for use in the present system by coupling them with lipid materials (i.e. referred to as an oil-compatible therapeutic) to make them soluble in the oil carrier.

This invention is particularly applicable for therapeutic agents which are used to treat malabsorption problems, skin disorders (e.g. herpes, acne, psoriasis), prostaglandin-mediated conditions (e.g. thromboembolic, gastrosecretory, and pulmonary disorders), hemapoietic and hematogenic disorders such as anemias, immunodeficient and autoimmune conditions, and diseases of the digestive system because of the rapid and improved absorption which is provided.

This invention has been described by reference to particular examples and embodiments which are not intended to be limiting thereon. It is to be understood, however, that variations and modifications of this invention would be

apparent to one skilled in the art which are not intended to depart from the spirit and scope of this invention.

I CLAIM:

1. A stable oil-in-water emulsion comprising:

(a) droplets of one or more long-chain polyunsaturated fatty acid-containing animal or vegetable oils;

(b) water;

(c) one or more emulsifying agents;

(d) one or more stabilizing agents; and

(e) one or more antimicrobial agents, wherein the oil droplets are sized so as to be readily absorped into the lymphatic system of a mammal via the digestive tract.

2. The emulsion of Claim 1 further comprising a pH-stabilizing amount of an organic buffer pair.

3. The emulsion of Claim 2 wherein the buffer pair is citric acid-sodium citrate.

4. The emulsion of Claim 1 further comprising one or more fat-soluble biologically-active agents.

5. The emulsion of Claim 4 wherein the agent comprises a fat-soluble vitamin.

6. The emulsion of Claim 5 wherein the vitamin is a nutritionally effective amount of a vitamin selected from the group consisting of Vitamins A, E, D, K and mixtures thereof.

7. The emulsion of Claim 5 further comprising an amount of one or more amino acids in an amount effective to stimulate the immune system of the mammal.

8. The emulsion of Claim 7 wherein the amino acids is selected from the group consisting of l-lysine, l-arginine or mixtures thereof.

9. The emulsion of Claim 5 wherein the oil is selected from the group consisting of sesame oil, safflower oil, primrose oil, sunflower oil, fish oil, cottonseed oil, or mixtures thereof.

10. The emulsion of Claim 9 wherein the emulsifying agent is effective to suspend the droplets by means of a multimolecular film.

11. The emulsion of Claim 9 wherein the droplets are less than or equal to about 0.5 micrometers in diameter.

12. The emulsion of Claim 5 wherein the emulsifying agent is selected from the group consisting of acacia, gelatin, tragacanth, chondrus, pectin and mixtures thereof.

13. The emulsion of Claim 5 wherein the stabilizing agent is a C_2-C_8 polyhydric alcohol.

14. The emulsion of Claim 13 wherein the stabilizing agent is a mixture of glycerin and sorbitol.

15. The emulsion of Claim 4 wherein the agent is selected from the group consisting of a prostaglandin, a long-chain unsaturated fatty acid prostaglandin precursor, gossypol and 5-azacytidine.

16. The emulsion of Claim 5 further comprising an effective amount of an antioxidant.

17. A method of administering a therapeutically-effective amount of a fat-soluble biologically-active agent to a mammal by orally administering to said mammal an effective amount of the emulsion of Claim 4.

18. A method of administering a therapeutically-effective amount of a fat-soluble vitamin to a mammal suffering from a deficiency thereof by administering to said mammal an effective amount of the emulsion of Claim 5.

19. The method of Claim 17 wherein the agent is 13-cis-retenoic acid.

20. A stable vitamin emulsion in water adapted to be rapidly absorbed through cell walls comprising:

(a) water in an amount sufficient to form the continuous phase in said emulsion,

(b) an oil soluble vitamin selected from the group consisting of A, D, E, K their pharmacologically stable derivatives, and mixtures thereof, in a therapeutically effective amount;

(c) a digestible vegetable oil carrier for said vitamin comprising long-chain unsaturated fatty acids compatible with, and in an amount greater than said vitamin, wherein the combined amount of vitamin and carrier is at least ten percent less than the amount of water; and

(d) a digestible emulsifier in an amount to maintain said vitamin and carrier in a stable emulsion in said water.

21. The product of claim 20 wherein a mixture of said vitamin and carrier comprise emulsified particles in said

water having a particle size approximately below about chylomicron size.

22. The product of claim 21 comprising an antimicrobial agent, a buffering agent, and an emulsion stabilizer.

23. The product of claim 22 comprising amino acids.

24. The product of claim 23 comprising a fatty acid derivative of abscorbic acid.

25. The product of claim 23 wherein said oil is selected from the group consisting of sesame and primrose, said emulsifier is gum acacia said antimicrobial agent is an alkyl paraben and benzoate said buffering agent is a citrate with citric acid said emulsion stabilizer is glycerine and sorbitol, and said amino acids are lysine and arginine.

26. The product of claim 25 comprising: about 40-50% water, about 10-30% oil, about 10-30% emulsifier, about 0.05-1.0% antimicrobial agent about 0.25-2.5% buffering agent, about 5-10% emulsion stabilizer, and about 0.25-2% amino acids.

27. A method of administering oil soluble therapeutic products which comprising mixing said therapeutic with an oil carrier and an emulsifying agent, adding said mixture to water and applying a high shear force to form an emulsion having a particle size below about a chylomicron, and orally administering the emulsion.

28. The method of claim 2 wherein said high shear force is applied by passing the mixture and water through a homogenizer to form an emulsion and then passing said emulsion through the homogenizer at least once again to reduce the size of the emulsified particles.

29. The method of forming a stable oil-in-water emulsion of an oily therapeutic adapted for oral administration and rapid absorption which comprises forming an oil phase mixture of an oil-soluble therapeutic, an oil carrier, and an emulsifier; forming a water phase mixture of water, an emulsion stabilizer and an antimicrobial agent; combining and mixing said oil phase and water phase, and subjecting said mixture to a high shear force sufficient to form emulsified particles having a size less than about a chylomicron.

30. The method of claim 29 comprising:

(a) forming a homogeneous oil-phase mixture of one or more edible, polyunsaturated fat-containing animal or vegetable oils, one or more fat-soluble vitamins, and one or more amino acids, and one or more antioxidants;

(b) adding an emulsifying agent to the stirred mixture so as to form a homogeneous paste;

(c) adding an aqueous solution of one or more polyhydric alcohol stabilizing agents and one or more antimicrobial agents to said stirred paste;

(d) adding a concentrated aqueous solution of organic buffering agents to said paste with slow stirring to form a buffered mixture; and

(e) passing the buffered mixture through a high-pressure homogenizer at about 4000-6000 psi, whereby the emulsified oils and vitamins possess a droplet size within the chylomicron-size range which allows their facile lymphatic absorption in the proximal intestine.

31. A method of treating human afflictions with an oil soluble or oil compatible therapeutic agent which comprises administering the therapeutic in an oil carrier as an emulsified particle in an aqueous phase wherein the

emulsified particle has a size no greater than about chylomicron size to facilitate adequate direct lymphatic absorption in the lacteals.

32. The method of claim 31 wherein the emulsified particle comprises an oil high in prostaglandin precursors and a compatible emulsifier wherein the emulsifier and oil are present in an amount within about twenty percent of each other by weight, and the combined weight of emulsifier and oil is from one to twenty percent less than the weight of the water.

33. The method of claim 31 wherein the human affliction is selected from the group consisting of thromoembolic disorders, pancreatic insufficiency, hemapoietic and hematogenic disorders, eruptive and proliferating skin diseases, immunodeficient, and autoimmune diseases.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01921

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3] A61K:31/07,A61K:31/11,A61K:31/12, A61K:31/59

U.S.[3] 424/180,424/236,424/284,424/317,424/319,424/331 (cont'd)

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/180, 424/236, 424/284, 424/317, 424/319, 424/331, 424/333, 424/344, 424/365

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

Chemical Abstract; Vitamin A, Vitamin D, Vitamin E, Vitamin K, acacia, gelatin, tragacanth, sorbitol, lysine, arginine

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,Y	U.S.,A, 3,067,104 published 04 December 1962, Hochberg et al.	1-33
X,Y	U.S.,A, 3,089,823 published 14 May 1963 Czarnecki	1-33
X,Y	U.S.,A, 3,138,532 published 23 June 1964 Aiello et al.	1-33
X,Y	U.S.,A, 3,143,475 published 04 August 1964, Koff et al.	1-33
X,Y	U.S.,A, 3,253,992 published 31 May 1966 Brooks	1-33
X,Y	U.S.,A, 3,773,930 published 20 November 1973, Mohammed et al.	1-33
X,Y	U.S.,A, 4,005,196 published 25 January 1977, Jandacek et al.	1-33
X,Y	U.S.,A, 4,075,333 published 21 February 1978, Josse	1-33

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
02 March 1984	08 MAR 1984
International Searching Authority [1]	Signature of Authorized Officer [19]
ISA/US	Douglas W. Robinson

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
X,Y	U.S.,A, 4,201,235 published 06 May 1980 Ciavatta	1-33
A	U.S.,A, 4,214,000 published 22 July 1980 Papa	17-19,31,33
X,Y	U.S.,A, 4,284,630 published 18 August 1981 Yu et al.	1-33
A	U.S.,A, 4,297,341 published 27 October 1981, Waller et al.	1,4,15
X,Y	GB, A, 2,075,458A published 18 November 1981, Rowe et al.	1-33
X,Y	DE, A, 2,936,252 published 20 March 1980 Harada et al.	1-33
X,Y	N, Chemical Abstract, Volume 86, No. 12, issued 21 March 1977,(Columbus, Ohio, USA), Abstract No. 86:78627e, Popovici, "Vitamin A and D stability in solutions"	1-33
X,Y	N, Chemical Abstract, Volume 92, No.10, issued 10 March 1980 (Columbus,Ohio, USA), Abstract No. 92:82322t, Cadorniga et al., "Stability of vitamin A acetate in microcapsules"	1-33
P	N, Chemical Abstract, Volume 99, No.4, issued 25 July 1983, (Columbus, Ohio, USA), Abstract No. 99:28036j, Asahi "Stable emulsions or solutions"	1-33
T	N, Chemical Abstract, Volume 100, No.6, issued 6 February 1984, (columbus, Ohio,USA), Abstract No. 100:39628u, Richter et al., "Concentrated hydrosols containing lipophilic and hydrophilic vitamins	1-33

INTERNATIONAL SEARCH REPORT

PCT/US83/01921

Classification of subject matter continued:

IPC:[3] A61K:31/70, A61K: 31/195, A61K:31/355, A61K:47/00

U.S.: 424/333, 424/344, 424/365